

PATENT COOPERATION TREATY

PCT

REC'D 09 MAR 2001

WIPO

EPO

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference A0000060-01-MJA	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/17039	International filing date (day/month/year) 21/06/2000	Priority date (day/month/year) 02/07/1999
International Patent Classification (IPC) or national classification and IPC A61K31/195		
<p>Applicant WARNER-LAMBERT COMPANY et al.</p> <p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 4 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p> <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input checked="" type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application 		

Date of submission of the demand 13/01/2001	Date of completion of this report 06.03.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Cattell, James Telephone No. +49 89 2399 8468



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/17039

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).*):

Description, pages:

1-11 as originally filed

Claims, No.:

1-9 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/17039

- the drawings, sheets:
5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):
(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1-9
	No: Claims
Inventive step (IS)	Yes: Claims 1-9
	No: Claims
Industrial applicability (IA)	Yes: Claims 1-9
	No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the

claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/17039

V.

- 1). Document D1 (WO 99/08667) discloses compositions with either gabapentin or pregabalin (see claims 1 and 7 and examples). The combined use is not disclosed.

It would not be obvious from D1 that the combination could synergistically be used to treat pain.

The claims therefore appear to meet the requirements of Articles 33(2) and (3) PCT.

VI.

DE 198,02327, Priority 23.01.98, published 29.07.99

WO 00/61188, Priority 09.04.99, published 19.10.00 (not cited in search report).

VIII.

- 2). For the assessment of the present claims 6-9 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION
(PCT Rule 61.2)

Date of mailing (day/month/year) 27 February 2001 (27.02.01)	To: Commissioner US Department of Commerce United States Patent and Trademark Office, PCT 2011 South Clark Place Room CP2/5C24 Arlington, VA 22202 ETATS-UNIS D'AMERIQUE in its capacity as elected Office
International application No. PCT/US00/17039	Applicant's or agent's file reference A0000060-01
International filing date (day/month/year) 21 June 2000 (21.06.00)	Priority date (day/month/year) 02 July 1999 (02.07.99)
Applicant BRUMMEL, Roger, N. et al	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

13 January 2001 (13.01.01)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Zakaria EL KHODARY Telephone No.: (41-22) 338.83.38
---	--

GÖDECKE AKTIENGESELLSCHAFT BERLIN

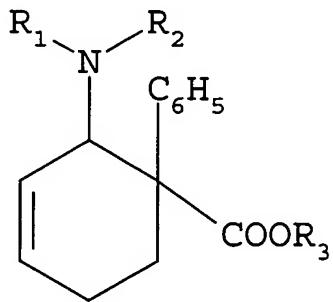
PD6375

Synergistic medicinal composition with analgesic action

Description

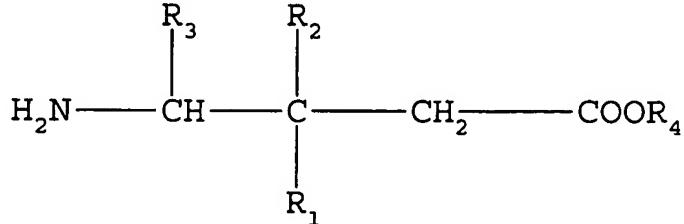
The invention concerns synergistic medicinal compositions with analgesic action containing an active material combination consisting of

- a) a basic-substituted cyclohexene of the general formula I



wherein R₁ and R₂, which can be the same or different, signify an alkyl radical with 1 to 6 C-atoms or two alkylene radicals linked with one another and R₃ an alkyl radical with 1 to 6 C-atoms and □

- b) a glutamic acid or gamma-aminobutyric acid analogue of the general formula II



wherein R₁ signifies a straight-chained or branched alkyl radical with 1 to 6 C-atoms, phenyl or cycloalkyl with 3 to 6 C-atoms, R₂ hydrogen or methyl or R₁ and R₂, together with the C-atom, signify cycloalkyl with 4 to 6 C-atoms, R₃ is hydrogen, methyl or carboxyl and R₄ is hydrogen or an alkyl group with 1 to 6 C-atoms, as well as pharmacologically compatible and pharmaceutically acceptable salts of the compounds of the general formula I and II.

Compounds of the general formula I are preferred in which R₁ and R₂ are the same or different and signify hydrogen or a methyl group and R₃ an ethyl group. Especially preferred are (\pm)-ethyl-(trans-2-dimethylamino-1-phenyl-3-cyclohexen-trans-1-carboxylate (tilidine) and (\pm)-ethyl-(trans-2-(methylamino)-1-phenyl-3-cyclohexene-trans-1-carboxylate (nortilidine) or their enantiomers, as well as their salts, preferably the hydrochloride or the dihydrogen orthophosphate.

Preferred compounds of the general formula II are those in which R₁ is hydrogen, R₂ an isobutyl group or R₁ and R₂, together with the C-atom, a cyclohexyl group and R₃ and R₄ is hydrogen. Especially preferred are aminomethyl-1-cyclohexane-acetic acid (gabapentin), 3-aminomethyl-5-methylhexanecarboxylic acid and ist enantiomer (S)-3-aminomethyl-5-hexanecarboxylic acid (pregabalin).

Compounds of the general formula I are known from DE-A 1 518 959, compounds of the general formula II are described, for example, in WO 93/23383 for the treatment of epileptic attacks.

Because of the basic nature of the compounds of the general formula I, salts of the acidic compounds of the general formula II are also formed directly.

The compounds of the general formulae I and II, as well as their salts or addition salts of both can be used in usual compositions and in mixtures with usual pharmaceutically acceptable carriers or dilution agents.

The compositions according to the invention can be administered orally, topically or parenterally in liquid or solid form. As

injection solution, above all water is used which contains the additives usual in the case of injection solutions, such as stabilising agents, solubilising agents or buffers.

The compositions can be present as usual galenical formulations, such as e.g. tablets, capsules, dragees, plasters, emulsions or salves. They are prepared in that one incorporates the compounds or their salts in per se known manner into a pharmacologically acceptable carrier material and possibly suitable additives.

Such additives are e.g. tartrate or citrate buffers, ethanol, complex formers (such as ethylene-diamine-tetraacetic acid and its non-toxic salts), as well as high molecular polymers (such as liquid polyethylene oxide) for viscosity regulation. Solid carrier materials are e.g. starch, lactose, mannitol, methyl cellulose, talc, highly dispersed silicic acids, high molecular fatty acids (such as stearic acid), gelatine, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats, solid high molecular polymers (such as polyethylene glycol); compositions suitable for oral administration can, if desired, also contain additional flavouring and/or sweetening materials.

Compounds of the general formula I, especially tilidine, possess an average analgesic potency. The action of tilidine can admittedly be increased in limited way by increasing of the dosage but, in the case of greatest pains, must be exchanged for more potent active materials, such as e.g. morphine.

The structural analogues of glutamic or gamma-aminobutyric acid according to general formula II, especially gabapentin and pregabalin, are known for their effectiveness in the case of cerebral convulsive attacks. In the case of the clinical use of gabapentin, it is found that this additionally possesses an analgesic effectiveness, especially in the case of neuropathic pains, whereby, however, the action mechanism is still not clarified.

Surprisingly, it has been found that the combination of both active materials permits a distinctly lower dosing than the individual

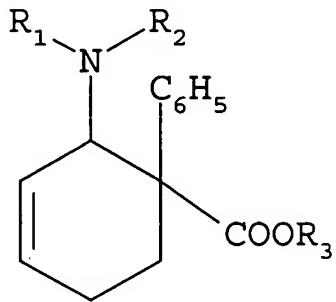
use, whereby an analgesic action is exhibited which exceeds by far the maximum action of the individual components and is thus more than additive. In addition, it has been found that an active material combination according to the invention is intrathecally administratable and, in contradistinction to the compounds of the general formula I which, administered in this way, are ineffective, exhibit an unexpectedly high analgesic action which, in comparison with the normal enteral or parenteral administration, makes possible a further considerable reduction of the amount of active material used.

With the active material combination according to the invention, there are made available extremely potent analgesic medicinal combinations with minimal side effects, the analgesic potency of which lies in the range of strong opioids, such as morphine or fentanyl. Due to the synergistic action of the combination, which above all has an effect on the compounds of formula I, the dosaging of these components can be kept very low. This has the additional advantage that the risk of misuse is considerably reduced and a development of tolerance, as well as the possible euphorising effect of strong analgesics, is countered. Therefore, by means of the combination according to the invention, there is made available a medicament superior to all hitherto strong analgesics since compounds of the formula II do not show these undesired properties of conventional strong analgesics.

Claims

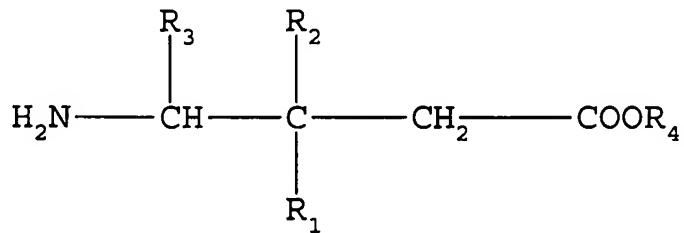
1. Medicinal composition with analgesic action, containing an active material combination consisting of

a) a substituted cyclohexen of the general formula I



wherein R_1 and R_2 , which can be the same or different, signify an alkyl radical with 1 to 6 C-atoms or two alkylene radicals linked with one another and R_3 an alkyl radical with 1 to 6 C-atoms and

b) a glutamic acid or gamma-aminobutyric acid analogue of the general formula II



wherein R_1 signifies a straight-chained or branched alkyl radical with 1 to 6 C-atoms, phenyl or cycloalkyl with 3 to 6 C-atoms, R_2 hydrogen or methyl or R_1 and R_2 , together with the C-atom, signify cycloalkyl with 4 to 6 C-atoms, R_3 is hydrogen, methyl or carboxyl, and R_4 is hydrogen or an alkyl group with 1 to 6 C-atoms, as well as pharmacologically

compatible and pharmaceutically acceptable salts of the compounds of the general formula I and II.

2. Medicament according to claim 1, characterised in that, for compounds of the general formula I, R₁ and R₂ are the same or different and signify hydrogen or a methyl group and R₃ an ethyl group and, for compounds of the general formula II, R₁ signifies hydrogen, R₂ an isobutyl group or R₁ and R₂, together with the C-atom, signify a cyclohexyl group and R₃ and R₄ hydrogen.

3. Medicaments according to claim 1 or 2, containing

- a) tilidine and/or nortilidine and
- b) gabapentin and/or pregabalin.

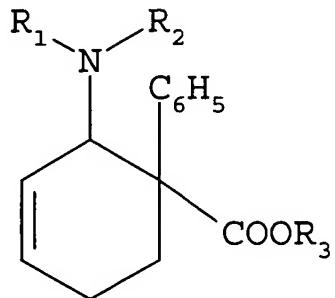
4. Medicaments according to claims 1 to 3 containing the pharmacologically most effective enantiomers of the components.

5. Use of compounds of the general formulae I and II according to claims 1 to 4 for the preparation of medicaments for the treatment of pain.

Summary

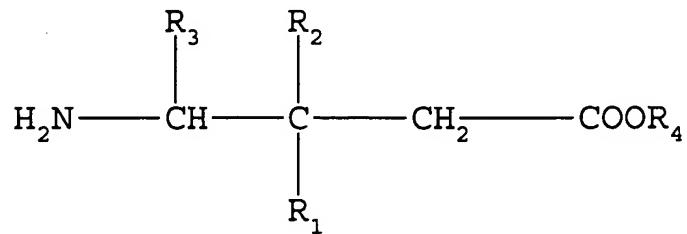
The invention concerns synergistic medicinal compositions with analgesic action containing an active material combination consisting of

- a) a substituted cyclohexene of the general formula I



and

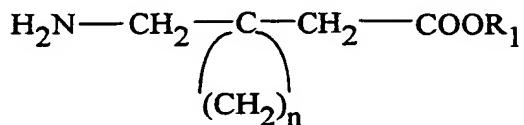
- b) a glutamic acid or gamma-aminobutyric acid analogue of the general formula II



A SYNERGISTIC COMBINATION: GABAPENTIN AND PREGABALIN

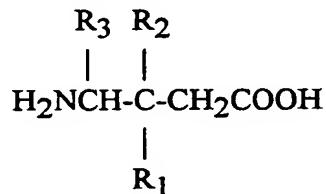
BACKGROUND OF THE INVENTION

Compounds of formula



5 wherein R₁ is hydrogen or a lower alkyl radical and n is 4, 5, or 6 are known in
 United States Patent Number 4,024,175 and its divisional United States Patent
 Number 4,087,544. The uses disclosed are: protective effect against cramp
 induced by thiosemicarbazide; protective action against cardiazole cramp; the
 cerebral diseases, epilepsy, faintness attacks, hypokinesia, and cranial traumas;
 10 and improvement in cerebral functions. The compounds are useful in geriatric
 patients. The patents are hereby incorporated by reference.

Compounds of formula



15 or a pharmaceutically acceptable salt thereof wherein R₁ is a straight or branched
 alkyl group having from 1 to 6 carbon atoms, phenyl or cycloalkyl having from
 20 3 to 6 carbon atoms; R₂ is hydrogen or methyl; and R₃ is hydrogen, or carboxyl
 are known in United States Patent Number 5,563,175 and its various divisionals.
 These patents are hereby incorporated by reference.

SUMMARY OF THE INVENTION

25 The instant invention is a pharmaceutical composition of synergistic effect
 which comprises a therapeutically effective amount of gabapentin or a

-2-

pharmaceutically acceptable salt or hydrate thereof and therapeutically effective amount of pregabalin or a pharmaceutically acceptable salt or hydrate thereof.

The pharmaceutical composition comprises gabapentin in the form of the free acid and pregabalin is in the form of the free acid.

5 The pharmaceutical composition is gabapentin in a ratio of 1:1000 and pregabalin is from 1:1000.

The pharmaceutical composition with a ratio of gabapentin to pregabalin from 1:1 to 1000:1 by weight.

10 The preferred pharmaceutical composition with a ratio from 1:1 to 250:1 by weight.

15 The invention is also a method for the treatment of pain in a mammal in need thereof comprising administering a therapeutically effective amount of gabapentin or a pharmaceutically acceptable salt or hydrate thereof and a therapeutically effective amount of pregabalin or a pharmaceutically acceptable salt or hydrate thereof in unit dosage form.

It is also a method for the treatment of pain in a mammal in need thereof comprising concomitant administration of gabapentin or a pharmaceutically acceptable salt or hydrate thereof and pregabalin or a pharmaceutically acceptable salt or hydrate thereof.

20 The method comprising administering gabapentin in the amount of from 5 to 250 mg and pregabalin in the amount of from 5 to 25 mg.

The range of the types of pain is wide including chronic and acute types.

BRIEF DESCRIPTION OF THE INVENTION

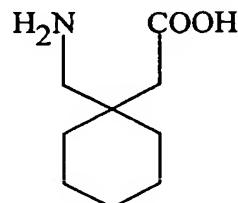
25 Figures 1 and 2 show the effect of a fixed dose 1:1 ratio of gabapentin and pregabalin on the maintenance of CITH.

Figures 3 and 4 show the effect of a fixed dose 10:1 ratio of gabapentin and pregabalin on the maintenance of CITH.

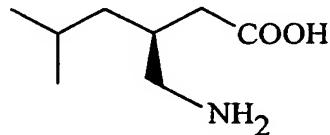
DETAILED DESCRIPTION OF THE INVENTION

Gabapentin is the generic name for the marketed product Neurontin®. The chemical name is 1-(aminomethyl)-cyclohexaneacetic acid. The chemical structure of the compound is:

5



Pregabalin is the generic name for (S)-3-(aminomethyl)-5-methylhexanoic acid. The chemical structure of the compound is:



It is also known as CI-1008 and as S-(+)-3-IBG.

10 Formerly, it was thought that gabapentin and pregabalin were the same in all pain models as one antagonist blocked both; therefore, a similar result was expected.

However, surprising differences have now been observed in an inflammatory model of pain.

15 The present invention relates to pharmaceutical comparisons and methods of using them. These comparisons have a synergistic effect in the treatment of pain. Advantages of these compositions include fewer side effects as lower dosages are needed. This increases patient compliance with the beneficial result of better control of pain.

20 The drugs can be administered together in the same dosage unit or can be prepared in separate dosage units administered at the same time. Different forms

-4-

of dosage units can be used, i.e., a tablet of gabapentin and an injection of pregabalin.

One particular advantage of the instant invention is the fact that no cross tolerance between the two compounds has been observed.

5 The synergistic composition of this invention utilizes any GABA analogs. A GABA analog is a compound derived from or based upon gamma-amino-butyric acid.

METHODS FOR COMBINATION STUDIES IN THE CARRAGEENAN-INDUCED THERMAL HYPERALGESIA MODEL

10 **Animals**

Male Sprague-Dawley rats (175-200 g), obtained from Bantin and Kingman (Hull, U.K.), were housed in groups of 6 under a 12-hour light/dark cycle (lights on at 07 h 00 min) with food and water ad libitum. All experiments were carried out by an observer unaware of drug treatments.

15 **Evaluation of Thermal Hyperalgesia**

Thermal hyperalgesia was assessed using the rat plantar test (Ugo Basile, Italy) following a modified method of Hargreaves K., Dubner R., Brown F., Flores C., and Joris J., A new and sensitive method for measuring thermal nociception in cutaneous hyperalgesia, *Pain* 1988;32:77-88. Male Sprague-Dawley rats (70-90 g) were habituated to the apparatus which consisted of three individual perspex boxes on an elevated glass table. A mobile radiant heat source located under the table was focused onto the desired paw and withdrawal latencies (PWL) recorded. PWLs were taken 3 times for both hind paws of each animal, the mean of which represented baselines for right and left hind paws. At least 5 minutes were allowed between each PWL for an animal. The apparatus was calibrated to give a PWL of approximately 10 seconds. There was an automatic cut-off point of 20 seconds to prevent tissue damage. After baseline PWLs were determined, animals received an intraplantar injection of carrageenan (100 µL of 20 mg/mL) into the right hind paw. PWL were reassessed following the same protocol as above 2 hours

-5-

postcarrageenan (this time point represented the start of peak hyperalgesia) to ascertain that hyperalgesia had developed. Test compounds were then administered as combinations at 2.5-hour post-carrageenan and PWL taken again at 1, 2, and 4-hour postdrug.

5 Combination Studies

Dose responses to gabapentin and pregabalin were first performed alone in the carrageenan-induced thermal hyperalgesia (CITH) model. The dose response data for both compounds were used to determine theoretical additive lines using the method described by Berenbaum M.C., What is synergy? *Pharmacological Reviews* 1989;41:93-141. Combinations of gabapentin and pregabalin were determined following a fixed ratio design, where the doses of both compounds vary in fixed dose ratios of 1:1 and 10:1. A dose response to the combination was performed following this design and compared to the theoretical additive line.

Drugs

15 Gabapentin and pregabalin were synthesised at Parke-Davis (Ann Arbor, USA). λ -Carrageenan were obtained from Sigma (Poole, UK). All compounds were dissolved in water except carrageenan which was dissolved in isotonic saline. Gabapentin and pregabalin combinations were administered in the same solution. Drug administrations were made in a volume of 1 mL/kg.

20 Data Analysis

Data for dose responses were subjected to a one-way analysis of variance (ANOVA) followed by a Dunnett's t-test. The dose response data for both compounds were used to determine theoretical additive lines as described by Berenbaum 1989.

25 The figures show the synergy between gabapentin and pregabalin by comparing the theoretical addition and the synergistic responses.

Figures 1 and 2. Effect of a 1:1 Fixed Dose Ratio of Gabapentin: Pregabalin on the Maintenance of Carrageenan-Induced Thermal Hyperalgesia. Dose response data for gabapentin and pregabalin alone (a). Fixed dose ratio of 1:1 gabapentin:pregabalin combination (b). The theoretical additive line was calculated from the dose response data in (a). All compounds were administered

-6-

P.O. and PWL to plantar test were examined 1-hour post drug administration.
Results are expressed as mean PWL(s) (vertical bars represent \pm SEM).

Figures 3 and 4. Effect of a 10:1 Fixed Dose Ratio of Gabapentin:
Pregabalin on the Maintenance of Carrageenan-Induced Thermal Hyperalgesia.
5 Dose response data for gabapentin and pregabalin alone (a). Fixed dose ratio of
10:1 gabapentin:pregabalin combination (b). Theoretical additive line was
calculated from the dose response data in (a). All compounds were administered
P.O. and PWL to plantar test were examined 1-hour post-drug administration.
Results are expressed a mean PWL(s) (vertical bars represent \pm SEM).

10 The instant invention is useful in a range of types of pain. It refers to acute
as well as chronic pain.

Acute pain is usually short-lived (e.g. postoperative pain). Chronic pain is
usually defined as pain persisting from 3 to 6 months and includes somatogenic
pains and psychogenic pains. Other types of pain are caused by injury or infection
15 of peripheral sensory nerves. It includes, but is not limited to pain from peripheral
nerve trauma, herpes virus infection, diabetes mellitus, causalgia, plexus avulsion,
neuroma, limb amputation, and vasculitis. Neuropathic pain is also caused by
nerve damage from chronic alcoholism, human immunodeficiency virus infection,
hypothyroidism, uremia, or vitamin deficiencies.

20 Psychogenic pain is that which occurs without an organic origin such as
low back pain, atypical facial pain, and chronic headache.

Other types of pain are: inflammatory pain, osteoarthritic pain, trigeminal
neuralgia, cancer pain, diabetic neuropathy, restless leg syndrome, acute herpetic
and postherpetic neuralgia, causalgia, brachial plexus avulsion, occipital
25 neuralgia, gout, phantom limb, burn, and other forms of neuralgia, neuropathic
and idiopathic pain syndrome.

A skilled physician will be able to determine the appropriate situation in
which subjects will find the synergistic combination useful.

The compounds of the present invention can be prepared and administered
30 in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the
present invention can be administered by injection, that is, intravenously,
intramuscularly, intracutaneously, subcutaneously, intraduodenally, or

intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise 5 as the active component, either a compound of Formula I or a corresponding pharmaceutically acceptable salt of a compound of Formula I.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, 10 suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

15 In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about 20 seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier 25 providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is 30 dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

5 Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired.

10 Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

15 Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

20 The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsules, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

25 The quantity of active component in a unit dose preparation may be varied within wide limits. For practical purposes, it is present in a concentration of about 10% in a solid composition and about 2% in a primary liquid composition. In medical use the drug may be administered 1 to 3 times daily as, for example, as capsules. The composition can, if desired, also contain other compatible therapeutic agents.

30 In therapeutic use, the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 1 mg to about 1000 mg/kg daily. A daily dose range of about 1 mg to about 500 mg/kg is

-9-

preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached.

5 For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

10 The relative amounts of the active ingredients in the combination may vary within a wide range.

The synergistic combination may contain a ratio of about 1:1 to about 1000:1; preferably 1:1 to 500:1 and particularly from 1:1 to 250:1 parts by weight of gabapentin or a pharmaceutically acceptable salt or hydrate thereof to pregabalin or a pharmaceutically acceptable salt or hydrate thereof.

15 The synergistic compositions of the instant invention are prepared by methods known in the pharmaceutical industry. For example, the compositions may be prepared by admixing the active ingredient with inert, non-toxic carriers or diluents (e.g. cellulose, silicic acid, stearine, polyornyspyrsolidone, talc, starch, etc.). The compositions may also contain well known additives (e.g. emulsifying or suspending agents, dyes, salts for controlling the osmotic pressure, buffers, etc.)

20

The following examples are for illustrative purposes and are not intended to limit the scope of the invention.

EXAMPLES

Capsules

25 50 mg, 100 mg, 125 mg, 200 mg, 250 mg, 300 mg, or 400 mg
Gabapentin, 125 mg
Pregabalin, 50 mg
Lactose USP, Anhydrous q.s. or 250 g
Sterotex Powder HM, 5 g

30 Combine the compound and the lactose in a tumble blend for 2 minutes, blend for 1 minute with the intensifier bar, and then tumble blend again for

-10-

1 minute. A portion of the blend is then mixed with the Sterotex powder, passed through a #30 screen and added back to the remainder of the blend. The mixed ingredients are then blended for 1 minute, blended with the intensifier bar for 30 seconds, and tumble blended for an additional minute. The appropriately sized 5 capsules are filled with 141 mg, 352.5 mg, or 705 mg of the blend, respectively, for the 50 mg, 125 mg and 250 mg containing capsules.

Tablets

5 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, or 600 mg

Gabapentin, 200 mg

10 Pregabalin, 5 mg

Corn Starch NF, 200 g

Cellulose, Microcrystalline, 46 g

Sterotex Powder HM, 4 g

Purified Water q.s. or 300 mL

15 Combine the corn starch, the cellulose, and the compound together in a planetary mixer and mix for 2 minutes. Add the water to this combination and mix for one minute. The resulting mix is spread on trays and dried in a hot air oven at 50°C until a moisture level of 1 to 2 percent is obtained. The dried mix is then milled.

20

Injectables

Gabapentin, 125 mg

Pregabalin, 5 mg

Water for Injection USP, q.s.

25 The compound or a suitable salt thereof is dissolved in water and passed through a 0.2-micron filter. Aliquots of the filtered solution are added to ampoules or vials, sealed and sterilized.

-11-

Capsules

100 mg, 300 mg, 400 mg

Gabapentin, 95 mg

Pregabalin, 5 mg

5 Lactose

Corn Starch

Talc

Gelatin

Titanium Dioxide

10

Capsules

Gabapentin or Pregabalin 100 mg, 300 mg, 400 mg, 600 mg

Gabapentin: 100 mg and inactive ingredients gelatin and titanium dioxide

300 mg and inactive ingredients gelatin, titanium dioxide, and yellow iron oxide

15

400 mg and inactive ingredients gelatin, red iron oxide, titanium dioxide, and yellow iron oxide

The above amounts can be adjusted as needed.

-12-

CLAIMS

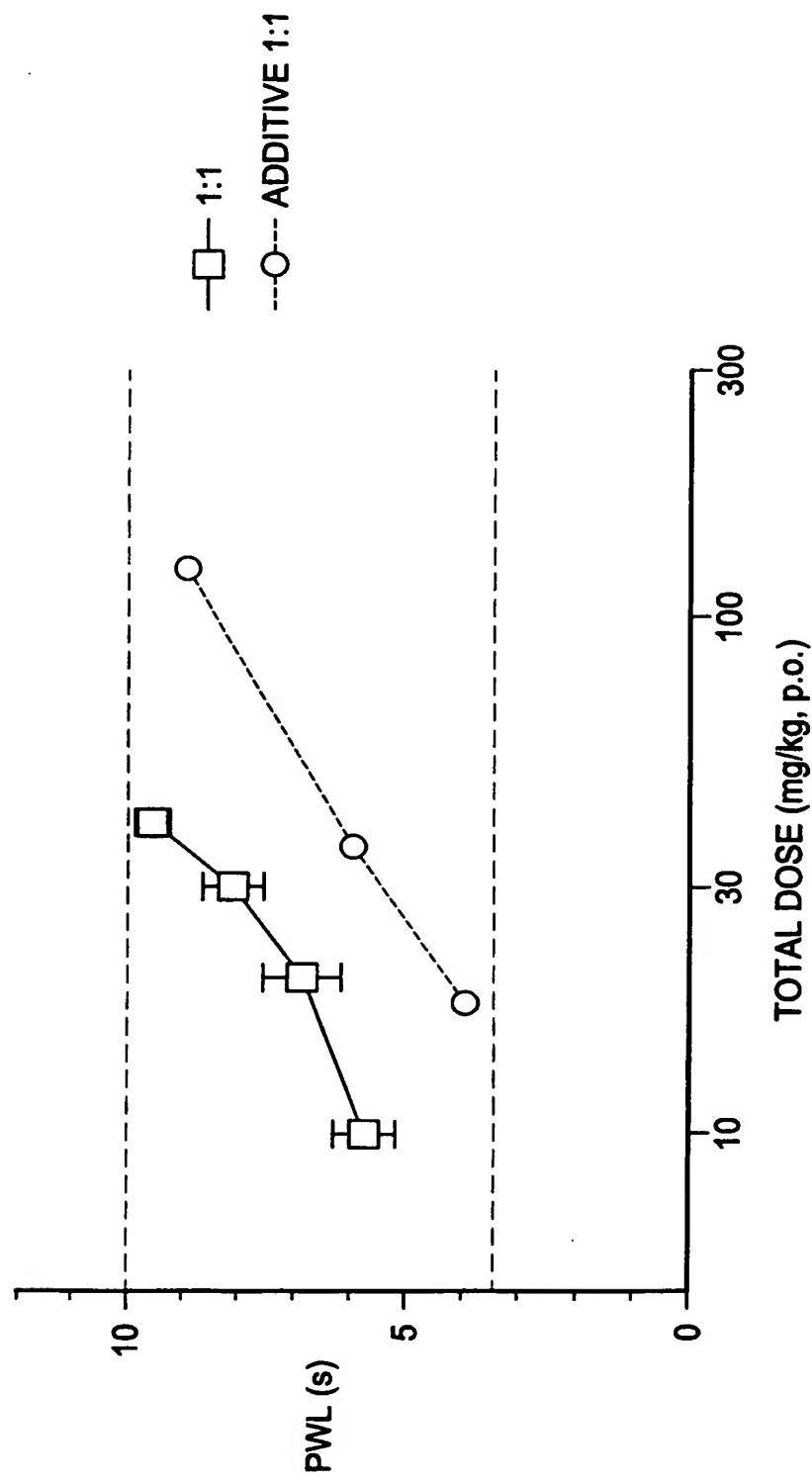
1. A pharmaceutical composition of synergistic effect which comprises a therapeutically effective amount of gabapentin or a pharmaceutically acceptable salt or hydrate thereof and therapeutically effective amount of pregabalin or a pharmaceutically acceptable salt or hydrate thereof.
5
2. A pharmaceutical composition according to Claim 1 which comprises gabapentin in the form of the free acid and pregabalin is in the form of the free acid.
3. A pharmaceutical composition according to Claim 1 wherein gabapentin is
10 in a ratio from 1:1000 and pregabalin is from 1:1000.
4. A pharmaceutical composition with a ratio of gabapentin to pregabalin from 1:1 to 1000:1 by weight.
5. A pharmaceutical composition with a ratio from 1:1 to 250:1 by weight.
6. A method for the treatment of pain in a mammal in need thereof comprising administering a therapeutically effective amount of gabapentin or a pharmaceutically acceptable salt or hydrate thereof and a therapeutically effective amount of pregabalin or a pharmaceutically acceptable salt or hydrate thereof in unit dosage form.
15
7. A method for the treatment of pain in a mammal in need thereof comprising concomitant administration of gabapentin or a pharmaceutically acceptable salt or hydrate thereof and pregabalin or a pharmaceutically acceptable salt or hydrate thereof.
20
8. A method according to Claim 7 wherein gabapentin is administered in the amount of from 5 to 250 mg and pregabalin in the amount of from 5 to
25 mg.

-13-

9. A method for the treatment of pain according to Claim 7 wherein the pain is selected from: hyperalgesia, allodynia, and inflammatory.

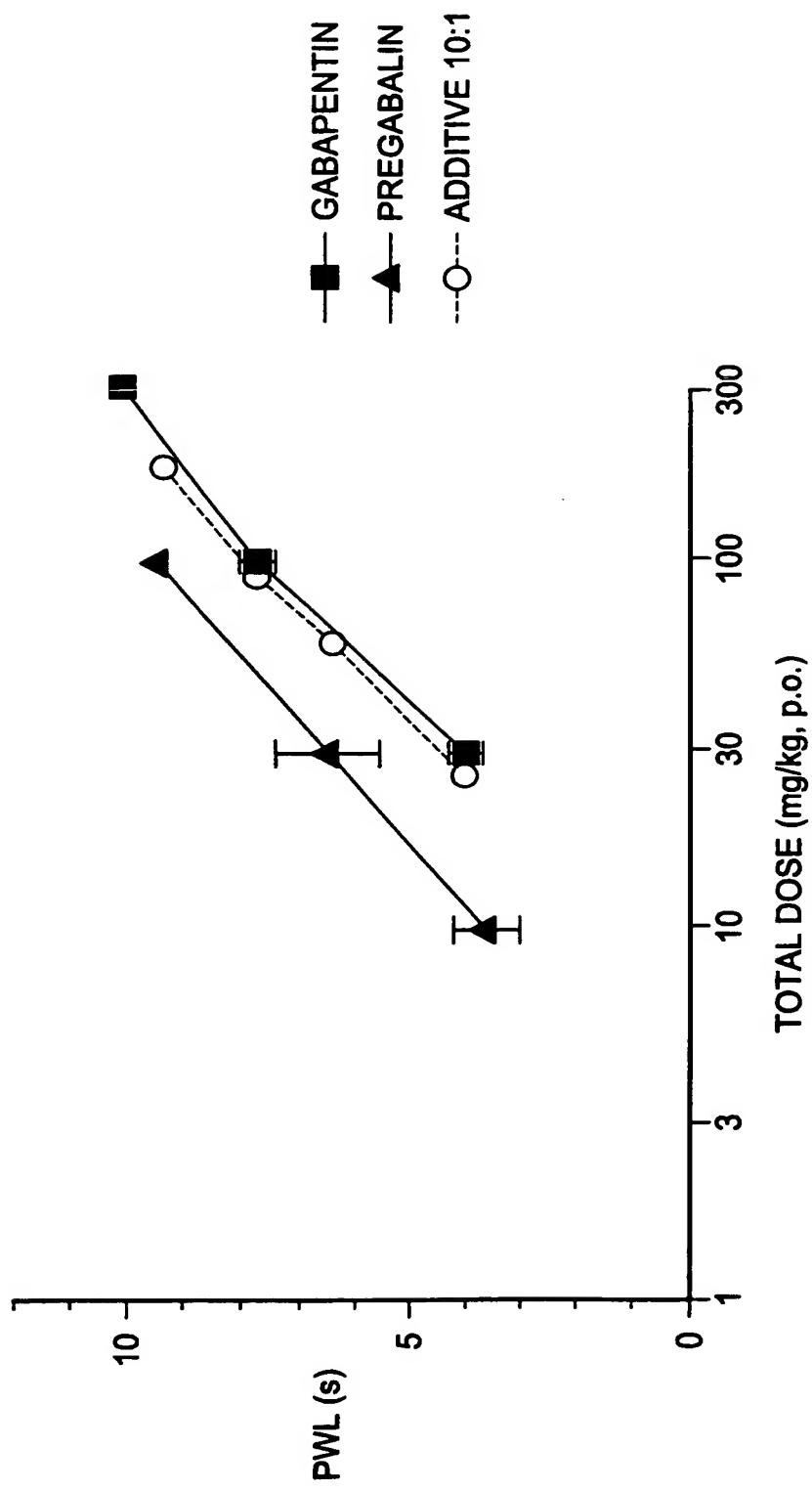
1/4

FIG. 1 1:1 GABAPENTIN / PREGABALIN (1h)



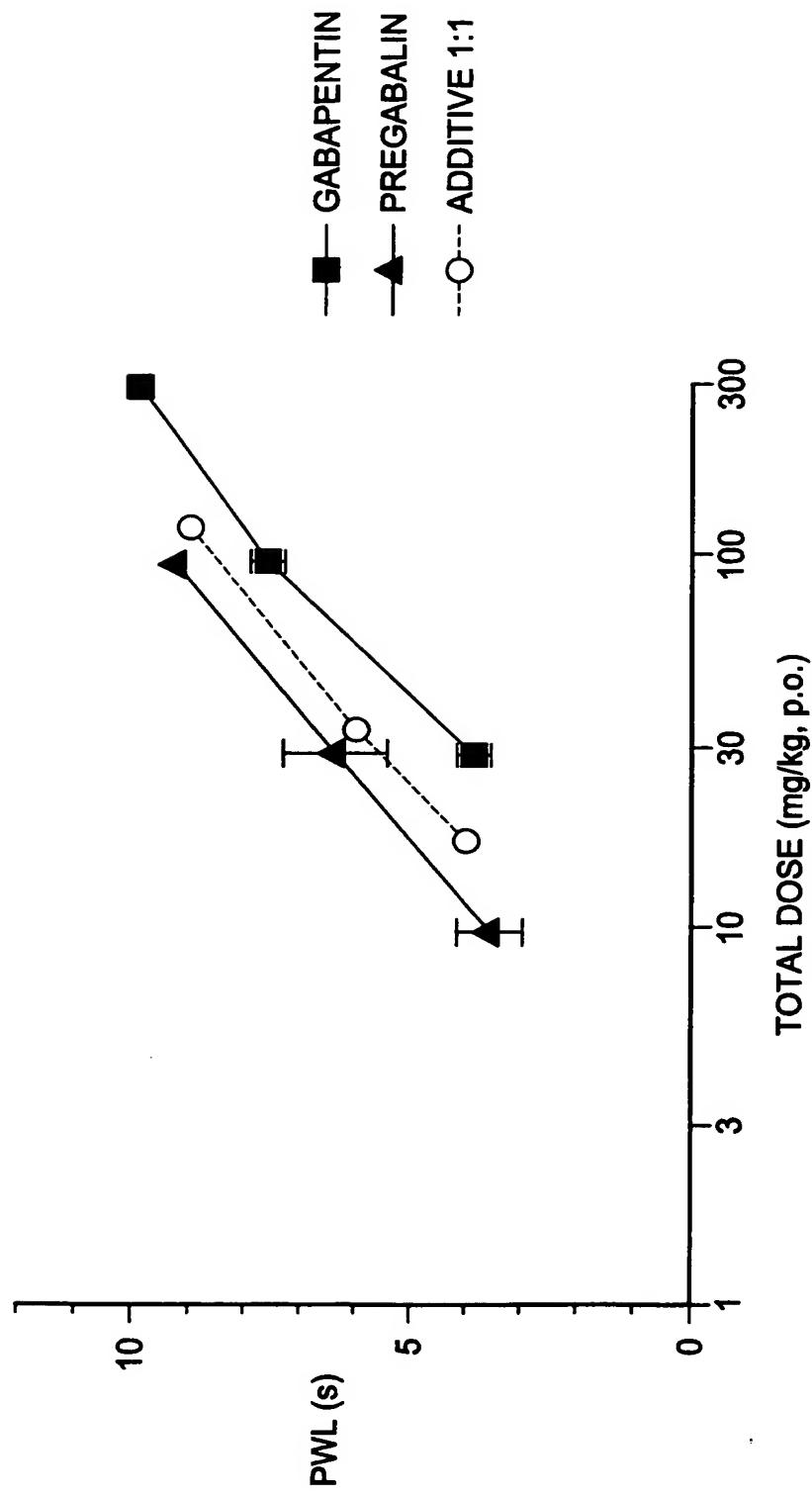
2/4

FIG. 2 DOSE RESPONSE FOR GABAPENTIN / PREGABALIN (1h)



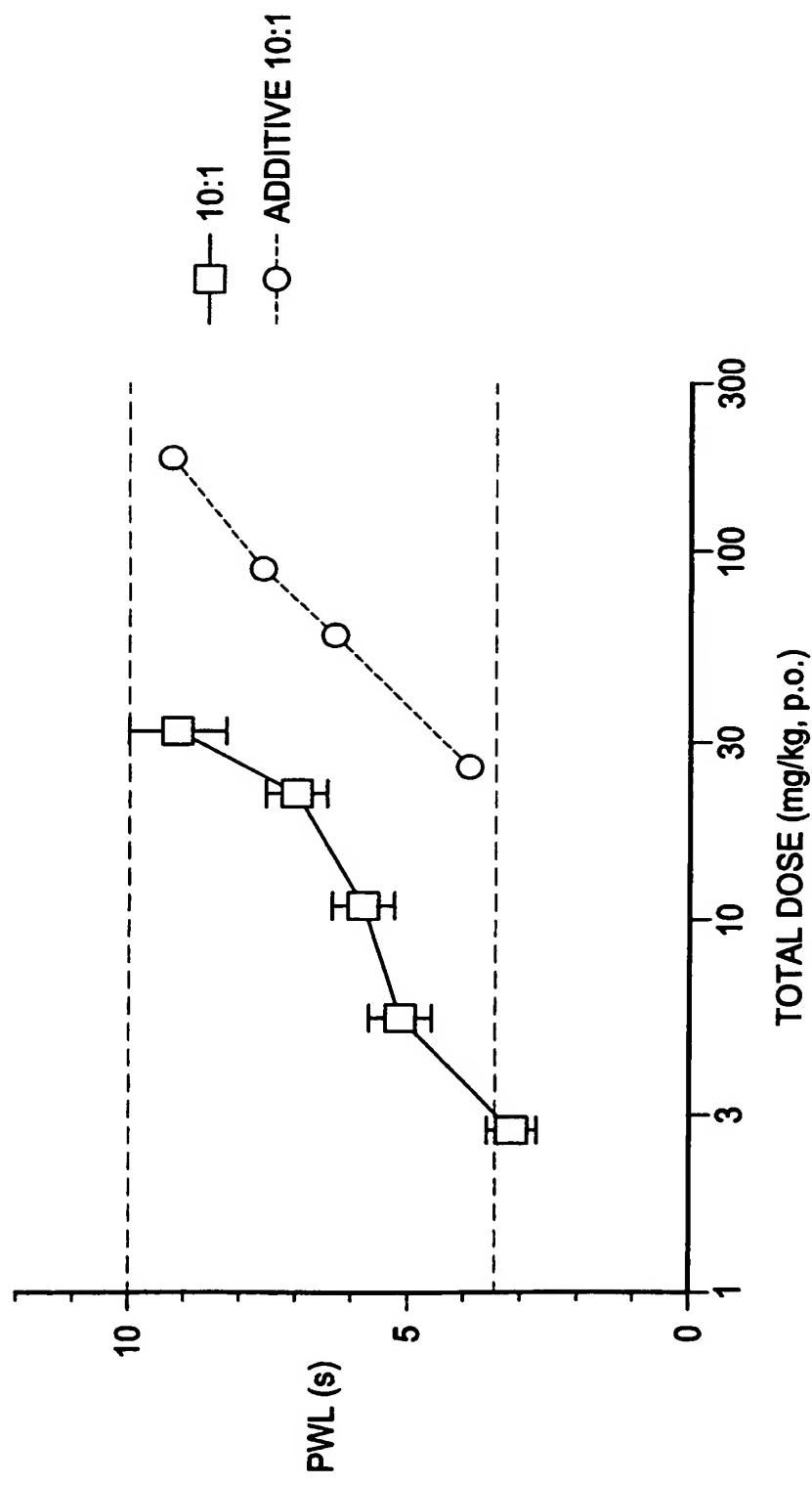
3/4

FIG. 3 DOSE RESPONSE FOR GABAPENTIN / PREGABALIN (1h)



4/4

FIG. 4 10:1 GABAPENTIN / PREGABALIN (1h)



INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/US 00/17039

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/195 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 08667 A (WARNER-LAMBERT) 25 February 1999 (1999-02-25) claims 1,5-7,11-13,17-19,23,24 page 7, line 7-13 example 1 -----	1-3,6,7
P,X	DE 198 02 327 A (GÖDECKE) 29 July 1999 (1999-07-29) claims 1-3,5 page 2, line 59-65 -----	1,3,6,7

Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

30 August 2000

Date of mailing of the international search report

06/09/2000

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentstaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Peeters, J

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. onal Application No

PCT/US 00/17039

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9908667 A	25-02-1999	AU ZA	9019198 A 9807439 A	08-03-1999 26-02-1999
DE 19802327 A	29-07-1999		NONE	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/17039

A. CLASSIFICATION OF SUBJECT MATTER
 IPC-7 A61K31/195 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 08667 A (WARNER-LAMBERT) 25 February 1999 (1999-02-25) claims 1,5-7,11-13,17-19,23,24 page 7, line 7-13 example 1 ---	1-3,6,7
P, X	DE 198 02 327 A (GÖDECKE) 29 July 1999 (1999-07-29) claims 1-3,5 page 2, line 59-65 -----	1,3,6,7

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

30 August 2000

06/09/2000

Name and mailing address of the ISA
 European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
 Fax: (+31-70) 340-3016

Authorized officer

Peeters, J

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/17039

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9908667 A	25-02-1999	AU ZA	9019198 A 9807439 A	08-03-1999 26-02-1999
DE 19802327 A	29-07-1999	NONE		



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 45/06, 31/195		A1	(11) International Publication Number: WO 00/53225 (43) International Publication Date: 14 September 2000 (14.09.00)
<p>(21) International Application Number: PCT/US00/02080</p> <p>(22) International Filing Date: 27 January 2000 (27.01.00)</p> <p>(30) Priority Data: 60/123,739 10 March 1999 (10.03.99) US</p> <p>(71) Applicant (<i>for all designated States except US</i>): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (<i>for US only</i>): HURTT, Mark, Richard [US/US]; 2903 Leslie Park Circle, Ann Arbor, MI 48105 (US). MUNDELL, Trevor [US/US]; 2300 Melrose, Ann Arbor, MI 48105 (US).</p> <p>(74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.</p>		<p>(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
<p>(54) Title: ANALGESIC COMPOSITIONS COMPRISING ANTI-EPILEPTIC COMPOUNDS AND METHODS OF USING SAME</p> <p>(57) Abstract</p> <p>The present invention is directed to novel combinations of one or more anti-epileptic compounds that demonstrate pain alleviating properties, with one or more compounds selected from the group consisting of analgesics, NMDA receptor antagonists, NSAIDs, and combinations thereof, and pharmaceutical compositions comprising same. It has been discovered that the administration of anti-epileptic compounds that demonstrates pain alleviating properties in these novel combinations results in an improved reduction in the frequency and severity of pain. It is also believed that the incidence of unwanted side effects can be reduced by these novel combinations in comparison to using higher doses of a single agent treatment to achieve a similar therapeutic effect. The present invention is also directed to methods of using effective amounts of the novel pharmaceutical compositions to treat pain in mammals.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China	KZ	Kazakhstan	PT	Portugal		
CU	Cuba	LC	Saint Lucia	RO	Romania		
CZ	Czech Republic	LI	Liechtenstein	RU	Russian Federation		
DE	Germany	LK	Sri Lanka	SD	Sudan		
DK	Denmark	LR	Liberia	SE	Sweden		
EE	Estonia			SG	Singapore		

ANALGESIC COMPOSITIONS COMPRISING ANTI-EPILEPTIC
COMPOUNDS AND METHODS OF USING SAME

FIELD OF THE INVENTION

The present invention is directed to novel combinations of anti-epileptic compounds that demonstrate pain alleviating properties, with compounds selected from the group consisting of analgesics, N-methyl-D-aspartate (NMDA) receptor antagonists and non-steroidal anti-inflammatory drugs (NSAIDs) and pharmaceutical compositions comprising same. It has been discovered that the administration of anti-epileptic compounds that demonstrate pain alleviating properties in these novel combinations results in an improved reduction in the frequency and severity of pain. It is also believed that the incidence of unwanted side effects can be reduced by these novel combinations in comparison to using higher doses of a single agent treatment to achieve a similar therapeutic effect.

The present invention is also directed to methods of using effective amounts of the novel pharmaceutical compositions to treat pain in mammals.

BACKGROUND OF THE INVENTION

A number of treatments involving the administration of single drugs are currently recommended for pain relief. The single administration of narcotic and non-narcotic analgesics and NSAIDs have been shown to display pain alleviating properties. Some anti-epileptics, such as gabapentin and pregabalin, have also demonstrated pain alleviating properties.

Despite the benefits derived from current single drug pain relief regimens, these regimens have disadvantages. One area of concern relates to the incidence of unwanted side effects caused by many of the pain treatment regimens available today. Narcotic analgesics, such as morphine, are sparingly prescribed for pain because of the well-known addictive effects and significant central nervous system (CNS) side effects and gastrointestinal side effects resulting from their single administration. Another class of drugs often used alone for treatment of

-2-

pain, non-steroidal anti-inflammatory drugs, such as ibuprofen and naproxen, are criticized for their irritation of the gastrointestinal tract.

Another concern of current pain treatment regimens relates to their effectiveness. Many single active ingredients employed in current pain relief 5 regimens cannot achieve adequate pain alleviation even at their maximum therapeutic approved doses in some severe pain states. In addition to not achieving adequate pain alleviation, increasing the drug dose may produce an increase in unwanted side effects such as cognitive impairment, nausea, and constipation.

In view of these concerns, it is evident that there is a need for an improved 10 pain regimen that provides an improved therapeutic benefit (ie, reduced severity and/or frequency of pain) and/or reduces the incidence of unwanted side effects caused by many of the current regimens.

SUMMARY OF THE INVENTION

The inventors have now surprisingly found that anti-epileptic compounds 15 having pain alleviating properties, when co-administered with compounds selected from the group consisting of analgesics, NMDA receptor antagonists, and NSAIDs, result in unexpected improved pain relief:

The present invention is directed to novel combinations for alleviating pain, the combinations comprising of anti-epileptic compounds, such as 20 gabapentin and pregabalin, that have displayed pain alleviating properties, and compounds selected from the group consisting of NMDA receptor antagonists, analgesics, and NSAIDs. It is also believed that the incidence of unwanted side effects can be reduced by co-administration of these compounds with anti-epileptic compounds having pain alleviating properties in comparison to using 25 higher doses of a single agent treatment to achieve a similar therapeutic effect.

The present invention is also directed to pharmaceutical compositions comprising the novel combinations of certain anti-epileptic compounds with compounds selected from the group consisting of NMDA receptor antagonists, analgesics, and NSAIDs. The active ingredients are combined with at least one 30 pharmaceutically acceptable carrier. The novel pharmaceutical compositions are

-3-

prepared in a wide variety of pharmaceutical delivery systems known to those of skill in the art, preferably oral and parenteral dosage forms.

The present invention is also directed to methods of treating mammals suffering from pain with the novel pharmaceutical composition to alleviate pain.

5 The method comprises the step of administering the pharmaceutical compositions comprising the novel anti-epileptic combinations to mammals in need of pain relief.

BRIEF DESCRIPTION OF THE FIGURES

10 Figure 1 shows the anti-hyperalgesic actions of fixed 1:1 (1 part by weight of gabapentin to 1 part by weight of naproxen sodium) combinations of gabapentin and naproxen sodium at various dosages.

Figure 2 shows the anti-hyperalgesic actions of fixed 50:1 (50 parts by weight of gabapentin to 1 part by weight of naproxen sodium) combinations of gabapentin and naproxen sodium at various dosages.

15 DETAILED DESCRIPTION OF THE INVENTION

It has now been unexpectedly found in accordance with the present invention that analgesic effects can be enhanced by the co-administration of one or more anti-epileptic compounds that demonstrate pain alleviating properties together with one or more compounds selected from the group consisting of 20 analgesics, NSAIDs, NMDA receptor antagonists, and combinations thereof. As used herein, the term "co-administration" is meant to include the administration of anti-epileptic compounds, before, during, or after administration of compounds selected from the group consisting of NMDA receptor antagonists, analgesics, and NSAIDs.

25 One advantage of using the novel combinations described herein is the reduced severity and/or frequency of pain. Another potential advantage is the overall improvement in pain control, which can include a reduction in the dosage and unwanted side effects.

-4-

Analgesics used in this invention can be, for example, non-narcotic analgesics or narcotic analgesic compounds.

Non-narcotic analgesics are generally defined to be those compounds that relieve pain without being addictive. A non-limiting example of a non-narcotic analgesic includes acetaminophen.

Narcotic analgesics are generally defined to be those compounds that are addictive when administered to treat a mammal for pain. Non-limiting examples of narcotic analgesics include opiates, opiate derivatives, opioids, and their pharmaceutically acceptable salts. Specific non-limiting examples of narcotic analgesics include alfentanil, alphaprodine, anileridine, bezitramide, codeine, dihydrocodeine, diphenoxylate, ethylmorphine, fentanyl, heroin, hydrocodone, hydromorphone, isomethadone, levomethorphan, morphine, neperidine, oxycodone, phenomorphan, phenoperidine, piritradide, pholcodine, proheptazonine, properidine, propiran, racemoramide, thebacon, trimeperidine, and the pharmaceutically acceptable salts thereof.

The expression "N-methyl-D-aspartate receptor" shall be understood to include all of the binding site subcategories associated with the NMDA receptor, e.g., the glycine-binding site, the phencyclidine (PCP)-binding site, etc., as well as the NMDA channel. The invention, herein contemplates the use of nontoxic substances that block or interfere with an NMDA receptor binding site. In one preferred embodiment NMDA receptor antagonists which can be used in the novel combinations are compounds that block or reduce the effects of NMDA at the NMDA subclass of neuronal glutamate receptors (non-limiting examples include dextrorphan, dextromethorphan, and ketamine) or that block or interfere with the NMDA channel (e.g., a substance that blocks the magnesium or calcium channel). In another preferred embodiment, the NMDA receptor antagonist is one which is specific for a subtype of NMDA receptor, those containing the NR2B subunit which are expressed in the forebrain (non-limiting examples include (1S,2S)-1-(4-hydroxyphenyl) 2-(4-hydroxy-4-phenylpiperidine)-1-propanol). Other NMDA receptor antagonists acting at other sites of an NMDA receptor include, but are not limited to GV-150526 (a compound in preclinical development by GlaxoWellcome), ifenprodil, and ACEA's 1168.

-5-

The term "NSAID", as used to describe other compounds useful in the novel combination herein, is intended to be a non-steroidal anti-inflammatory compound. NSAIDs are categorized by virtue of their ability to inhibit cyclooxygenase. Cyclooxygenase 1 and cyclooxygenase 2 are the two major isoforms of cyclooxygenase and most standard NSAIDs are mixed inhibitors of the two isoforms. Most standard NSAIDs fall within one of the following five structural categories: (1) propionic acid derivatives, such as ibuprofen, naproxen, naprosyn, diclofenac, and ketoprofen; (2) acetic acid derivatives, such as tolmetin and sulindac; (3) fenamic acid derivatives, such as mefenamic acid and 5 meclofenamic acid; (4) biphenylcarboxylic acid derivatives, such as diflunisal and flufenisal; and (5) oxicams, such as piroxim, sudoxicam, and isoxicam. Other useful NSAIDs include aspirin.

Another class of NSAID has recently been described which selectively inhibits cyclooxygenase 2. These compounds reduce pain and inhibit the 10 inflammatory response without damaging the gastric mucosa, a common toxicity observed with the mixed inhibitors. (Z)-5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2-imino-4-thiazolidinone methanesulfonate (1:1), celecoxib, meloxicam, and their pharmaceutically acceptable salts are examples of 15 selective cyclooxygenase 2 inhibitors.

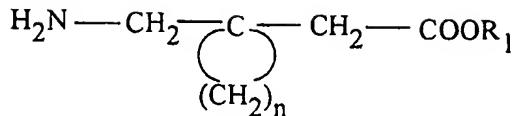
The term "anti-epileptic compound" is generally defined to be a pharmaceutically acceptable active ingredient that treats disorders characterized by recurring attacks of motor, sensory, or psychic malfunction with or without unconsciousness or convulsive movements. Non-limiting examples of 20 anti-epileptic compounds having analgesic activity include gabapentin, pregabalin, carbamazepine, lamotrigine, phenytoin, fosphenytoin, and analogues thereof.

The term "pain alleviating properties" is generally defined herein to include the expressions "pain-suppressing," "pain-reducing," and "pain-inhibiting" as the invention is applicable to the alleviation of existing pain, as well 25 as the suppression or inhibition of pain which would otherwise ensue from the imminent pain-causing event.

In a preferred embodiment of the present invention, anti-epileptic compounds having pain alleviating properties include those that have the

-6-

following Formula I:



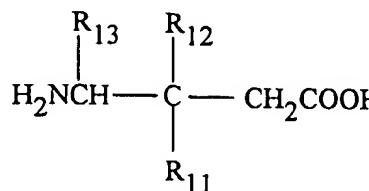
I

wherein R₁ is hydrogen or a lower alkyl; n is an integer of from 4 to 6; and the cyclic ring is optionally substituted, and the pharmaceutically acceptable salts thereof. The term lower alkyl includes straight or branched chain alkyl groups of up to eight carbon atoms. An especially preferred embodiment utilizes a compound of Formula I where R₁ is hydrogen and n is 5, which compound is 1-(aminomethyl)-cyclohexane acetic acid, known generically as gabapentin.

Other preferred compounds of Formula I above include, but are not limited to, ethyl 1-aminomethyl-1-cyclohexane-acetate, 1-aminomethyl-1-cycloheptane-acetic acid, 1-aminomethyl-1-cyclopentane-acetic acid, methyl-1-aminomethyl-1-cyclohexane-acetate, n-butyl 1-aminomethyl-1-cyclohexane-acetate, methyl 1-aminomethyl-1-cycloheptane-acetate, n-butyl 1-aminomethyl-1-cycloheptane-acetate, toluene sulfonate, 1-aminomethyl-1-cyclopentane-acetate, benzene-sulfonate, and n-butyl 1-aminomethyl-1-cyclopentane-acetate.

Other preferred compounds of Formula I above, wherein the cyclic ring is substituted for example with alkyl such as methyl or ethyl, include, but are not limited to (1-aminomethyl-3-methylcyclohexyl)acetic acid, (1-aminomethyl-3-methylcyclopentyl)acetic acid, and (1-aminomethyl-3,4-dimethylcyclopentyl)acetic acid.

In another preferred embodiment of the present invention, anti-epileptic compounds having pain alleviating properties include those that are included in Formula II:



II

wherein R₁₁ is a straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl having from 3 to 6 carbon atoms; R₁₂ is hydrogen or methyl; and

-7-

R₁₃ is hydrogen, methyl, or carboxyl; or an individual diastereomeric or enantiomeric isomer thereof; or a pharmaceutically acceptable salt thereof.

The most preferred compound of Formula II is where R₁₂ and R₁₃ are both hydrogen, and R₁₁ is -(CH₂)₀₋₂-iC₄H₉ as an (R), (S), or (R,S) isomer. A more preferred embodiment of the invention utilizes 3-aminomethyl-5-methylhexanoic acid, and especially (S)-3-(aminomethyl)-5-methylhexanoic acid, now known generically as pregabalin. Another preferred compound is 3-(1-aminoethyl)-5-methylhexanoic acid.

In the preferred embodiment of the present invention, the combination will be comprised of compounds of Formula I in combination with one or more compounds selected from the group consisting of NSAIDs, analgesics, NMDA receptor antagonists, and combinations thereof. In a more preferred embodiment of the present invention, the combination will contain the compound, gabapentin, as the anti-epileptic drug in combination with one or more compounds selected from the group consisting of NSAIDs, analgesics, NMDA receptor antagonists, and combinations thereof.

In one embodiment of the present invention, a single anti-epileptic compound is combined with a single compound selected from the group consisting of NSAIDs, analgesics, and NMDA receptor antagonists. While any anti-epileptic compound disclosed herein can be combined with any NSAID, analgesic, or NMDA receptor antagonist disclosed herein, the preferred anti-epileptic compound is gabapentin. Preferred combinations include, but are not limited to, gabapentin/opioid, gabapentin/morphine, gabapentin/hydrocodone, gabapentin/oxycodone, gabapentin/ibuprofen, gabapentin/naproxen, gabapentin/acetaminophen, pregabalin/opioid, pregabalin/morphine, pregabalin/hydrocodone, pregabalin/oxycodone, pregabalin/ibuprofen, pregabalin/naproxen, and pregabalin/acetaminophen.

In another embodiment of the present invention, a single anti-epileptic compound is combined with two or more, preferably two, compounds selected from the group consisting of NSAIDs, analgesics, NMDA receptor antagonists, or combinations thereof. While any anti-epileptic compound disclosed herein can be combined with any two compounds selected from NSAID, analgesic, NMDA

-8-

receptor antagonists, or combinations thereof, the preferred anti-epileptic compound is gabapentin. Preferred combinations include, but are not limited to, gabapentin/morphine/naproxen, gabapentin/opioid/NSAID, gabapentin/morphine/ibuprofen, gabapentin/hydrocodone/acetaminophen, gabapentin/oxycodone/acetaminophen, pregabalin/morphine/naproxen, pregabalin/opioid/NSAID, pregabalin/morphine/ibuprofen, pregabalin/hydrocodone/acetaminophen, pregabalin/oxycodone/acetaminophen,

In another embodiment of the present invention, two or more anti-epileptic compounds are combined with one or more compounds selected from the group consisting of NSAIDs, analgesics, NMDA receptor antagonists, or combinations thereof. While any anti-epileptic compounds disclosed herein can be combined with one or more compounds selected from NSAID, analgesic, NMDA receptor antagonists, or combinations thereof, the preferred anti-epileptic compounds are chosen from the compounds of Formulas I and II. Preferred combinations include, but are not limited to, gabapentin/pregabalin/opioid, gabapentin/pregabalin/NSAID, gabapentin/pregabalin/naproxen.

In addition to its pain alleviating properties, gabapentin is extremely well-tolerated and has been demonstrated to be virtually free of drug interactions. The unique properties and mechanism of action of anti-epileptic compounds like gabapentin, which demonstrate pain alleviating properties, would allow it to be used in the combinations described above with the benefit of providing better pain relief than if it were used not in combination. An added benefit of using the combination would be to use reduced quantities of medication, thereby potentially reducing adverse events for the patient.

The amount of the active ingredients in the combinations will vary depending on the mammal to which the combinations are administered, the type of pain to be treated, other active ingredients present, etc. Generally, the amount of the anti-epileptic compound(s) and the other active compound(s) for a given composition and dosage form can be readily determined employing routine procedures.

The present invention is also directed to methods of treating mammals to alleviate pain by the co-administration of one or more anti-epileptic compounds that have pain alleviating properties and one or more compounds selected from the

-9-

group consisting of analgesics, NSAIDS, NMDA receptor antagonists, and combinations thereof. Any of the combinations disclosed herein can be used for treatment. The types of treatable pain experienced by mammals is varied and known to medical practitioners. Non-limiting examples of mammalian pain 5 include centrally mediated pain, peripherally mediated pain, structural or soft tissue injury related pain, progressive disease related pain (i.e., oncology) and neuropathic pain states, all of which would include both acute (i.e., acute injury or trauma, pre- and post-surgical, headache such as a migraine), chronic (i.e., neuropathic pain conditions such diabetic peripheral neuropathy and post-hepatic 10 neuralgia) and inflammatory condition (i.e., osteo or rheumatoid arthritis, sequela to acute injury or trauma) pain states.

Pharmaceutical compositions containing the combinations of the present invention or their salts are produced by formulating the active compounds in dosage unit form with a pharmaceutical carrier. Some examples of suitable dosage 15 unit forms are tablets, capsules, pills, powders, aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions packaged in containers containing either one or some larger number of dosage units and capable of being subdivided into individual doses. Some examples of suitable pharmaceutical carriers, including pharmaceutical diluents, are gelatin capsules; sugars such as 20 lactose and sucrose; starches such as corn starch and potato starch; cellulose derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, methyl cellulose, and cellulose acetate phthalate; gelatin; talc; stearic acid; magnesium stearate; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and oil of theobroma; propylene glycol, glycerin, sorbitol; polyethylene 25 glycol; water, agar, alginic acid; isotonic saline, and phosphate buffer solutions; as well as other compatible substances normally used in pharmaceutical formulations. The compositions of the invention can also contain other components such as coloring agents, flavoring agents, and/or preservatives. These materials, if present, are usually used in relatively small amounts. The 30 compositions can, if desired, also contain other suitable pharmacologically active components.

-10-

Preferred routes of administration of the subject combinations are oral or parenteral. Dosing will vary depending upon the mammal and a number of other factors.

EXAMPLES

5 Example 1

The aim of this experiment was to characterize the antinociceptive and anti-inflammatory effects of gabapentin administered in combination with a prototypic NSAID in the rat. In this example, gabapentin, naproxen sodium, and the combination of gabapentin and naproxen sodium were evaluated in a standard 10 rat carrageenan footpad thermal hyperalgesia assay. This assay utilizes an extract of seaweed (carrageenan) that, when injected into the footpad of test animals, causes a sterile inflammation, thereby lowering the pain threshold. Anti-epileptic agents having analgesic properties, such as gabapentin, raise the pain threshold back to normal, thereby enabling the animal to tolerate an external source of pain 15 for a longer period of time relative to untreated control animals.

As shown in Figure 1, gabapentin and naproxen sodium were given alone (gabapentin at 120 min after dosing; naproxen sodium at 120 min after dosing). Each data point represents the mean and standard error of mean. Data for each drug were fitted by least squares linear regression to a straight line. The theoretical 20 dose-additive line for a 1:1 dose ratio was determined (dotted line) as described (Tallarida, 1992). The experimental determination of a 1:1 dose ratio was determined (gabapentin-naproxen sodium mixture 1:1) and was found to be significantly different than the theoretical dose-additive line. Thus, a supra-additive effect was determined for the combination of the two treatments given 25 simultaneously. As shown in Figure 2, the experiment was performed as described in Figure 1 and similarly a supra-additive effect was determined for the combination of the two treatments given simultaneously, except that the theoretical dose-additive line (dotted line) and experimental data (open boxes) were both determined for a 50:1 ratio of gabapentin dose to naproxen sodium 30 dose.

-11-

To summarize, the data showed that both gabapentin (3-100 mg/kg PO) and naproxen sodium (0.3-30 mg/kg PO) caused anti-hyperalgesic actions in the rat carrageenan footpad model (Hargreaves test). Combinations in a fixed ratio (1 mg gabapentin/1 mg naproxen sodium or 1:1 ratio) were anti-hyperalgesic, and produced a significantly supra-additive effect (synergistic action). For example, with a 1:1 dose ratio, dosages of naproxen sodium (0.05 mg/kg) plus gabapentin (0.05 mg/kg) that were both less than 1/10th of the ED₅₀ dose of the respective compounds alone, produced maximal anti-hyperalgesic effects when given in combination (see Table 1). Combinations in a fixed ratio (50 mg gabapentin/1 mg naproxen sodium) also were anti-hyperalgesic, with a significant tendency towards a greater than additive effect.

The data establish that the combination of gabapentin and naproxen sodium is synergistic in its ability to relieve acute and chronic pain. The data also establish that the most preferred combination of gabapentin plus naproxen sodium is in a fixed-ratio combination near 1:1 (within some reasonable limit).

Table 1. ED₅₀ Values Determined for Gabapentin, Naproxen and Two Fixed-Ratio Combinations in the Carrageenan Rat Footpad Thermal Hyperalgesia Test

Drug Treatment	ED ₅₀ †
Gabapentin	17 mg/kg (2.4 - 46 mg/kg)†
Naproxen sodium	0.36 mg/kg (0.007 - 1.26 mg/kg)†
Theoretical 1:1 (gabapentin:naproxen)	0.7 mg/kg combined total [0.35 mg/kg gabapentin plus 0.35 mg/kg naproxen]
Experimental 1:1 (gabapentin:naproxen)	0.00022 mg/kg combined total (n.d. - 0.0020)† [0.00011 mg/kg gabapentin plus 0.00011 mg/kg naproxen]**

-12-

Theoretical 50:1 (gabapentin:naproxen)	9.0 mg/kg combined total [8.8 mg/kg gabapentin plus 0.18 mg/kg naproxen]
Experimental 50:1 (gabapentin:naproxen)	0.77 mg/kg combined total (0.06 – 3.18 mg/kg)† [0.75 mg/kg gabapentin plus 0.015 mg/kg naproxen]*

† 95% confidence limits of experimental ED₅₀ values are shown in parentheses.

* Significantly less than additive theoretical combined ED₅₀, p < 0.05.

** Significantly less than additive theoretical combined ED₅₀, p < 0.001.

n.d. = not determined

5

METHODS

Animals

Male Sprague-Dawley rats (200-250 g, Sasco Laboratories) were used. Rats were group housed 5/cage on a 12-hour light:dark cycle with free access to food and water. Rats received only one dose of a drug or drug combination. All drugs were administered orally by gavage.

Experimental Design

Dose-effect curves were first determined for (1) gabapentin by itself and (2) a prototypic NSAID (e.g., naproxen) by itself. The ED₅₀ value and 95% confidence limits of each agent was determined, as was the time to peak effect.

After determination of these values, dose effect curves were generated for gabapentin administered in a fixed dose ratio with the NSAID; the drugs were administered so that their peak effects were coincident. ED₅₀ values and 95% confidence limits were then determined for the drugs in combination.

10

15

-13-

Measures of Antinociception

Carrageenan-induced thermal hyperalgesia: Rats were acclimated to a testing chamber whose glass floor was maintained at 25°C. Thirty minutes later, a high intensity beam of light was focused through the glass on the ventral surface of each hindpaw, and the latency to reflex withdrawal of the paw from the light beam was measured to the nearest 0.1 second. This latency was termed the paw flick latency (PFL). Two measurements of PFL spaced 20 minutes apart were made for each paw, and the second measurement was taken as the baseline response latency. After determination of baseline PFL, 100 µL of 2% lambda-carrageenan was injected in the plantar surface of one hindpaw and the animal returned to the testing chamber. Two hours later, when thermal hyperalgesia was maximal and stable, either vehicle, gabapentin, naproxen, or gabapentin and naproxen was administered by gavage. Response latencies for the ipsilateral and contralateral hindpaws were then re-determined 15, 30, 45, 60, 90 and 120 minutes later. Data for further analysis were taken 120 minutes after oral dosing.

Statistical Analysis

Data were expressed as the mean ± SEM. Two-way analyses of variance for repeated measures was used to compare the effects of drug to that of vehicle. Dose-effect lines for gabapentin and the NSAID were constructed using individual data and fitted with least squares linear regression analysis to determine ED₅₀ values and 95% confidence limits. A similar analysis was conducted for the drugs in combination using the total dose administered. Since parallel dose-effect lines were obtained for gabapentin, naproxen, and the combination of gabapentin and naproxen, then a parallel line assay was conducted as described by Tallarida (Tallarida, 1992; Tallarida, et al; 1989). This analysis compared the position of the experimentally-derived dose-effect line for the combination to the position of the theoretical dose-additive line. A significant shift to the left or the right of the theoretical dose-additive line indicates that the drugs interacted in a supra-additive (synergistic) or an infra-additive manner (antagonistic), respectively.

-14-

The preceding examples were presented so that the present invention may be better understood and are intended for purposes of illustration only and should not be construed to limit the scope of the invention, as defined by the claims appended hereto.

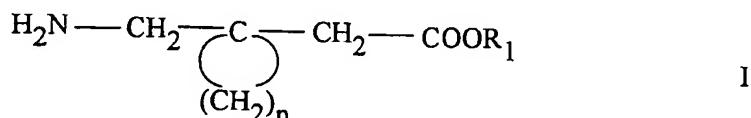
- 15 -

CLAIMS

What is claimed is:

- 5

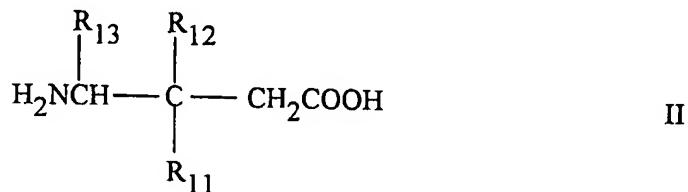
 1. A combination of an effective amount of at least one anti-epileptic compound having pain alleviating properties and an effective amount of at least one compound selected from the group consisting of NMDA receptor antagonists, NSAIDs, analgesics, and combinations thereof.
 2. The combination of Claim 1 wherein the anti-epileptic compound is a compound of Formula I



wherein R₁ is hydrogen or a lower alkyl; n is an integer of from 4 to 6; and the cyclic ring is optionally substituted, and the pharmaceutically acceptable salts thereof.

3. The combination of Claim 1 wherein the anti-epileptic compound is gabapentin.

15 4. The combination of Claim 1 wherein the anti-epileptic compound is a compound of Formula II



wherein R₁₁ is a straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl having from 3 to 6 carbon atoms; R₁₂ is hydrogen or methyl; and R₁₃ is hydrogen, methyl, or carboxyl; or an individual

-16-

diastereomeric or enantiomeric isomer thereof; or a pharmaceutically acceptable salt thereof.

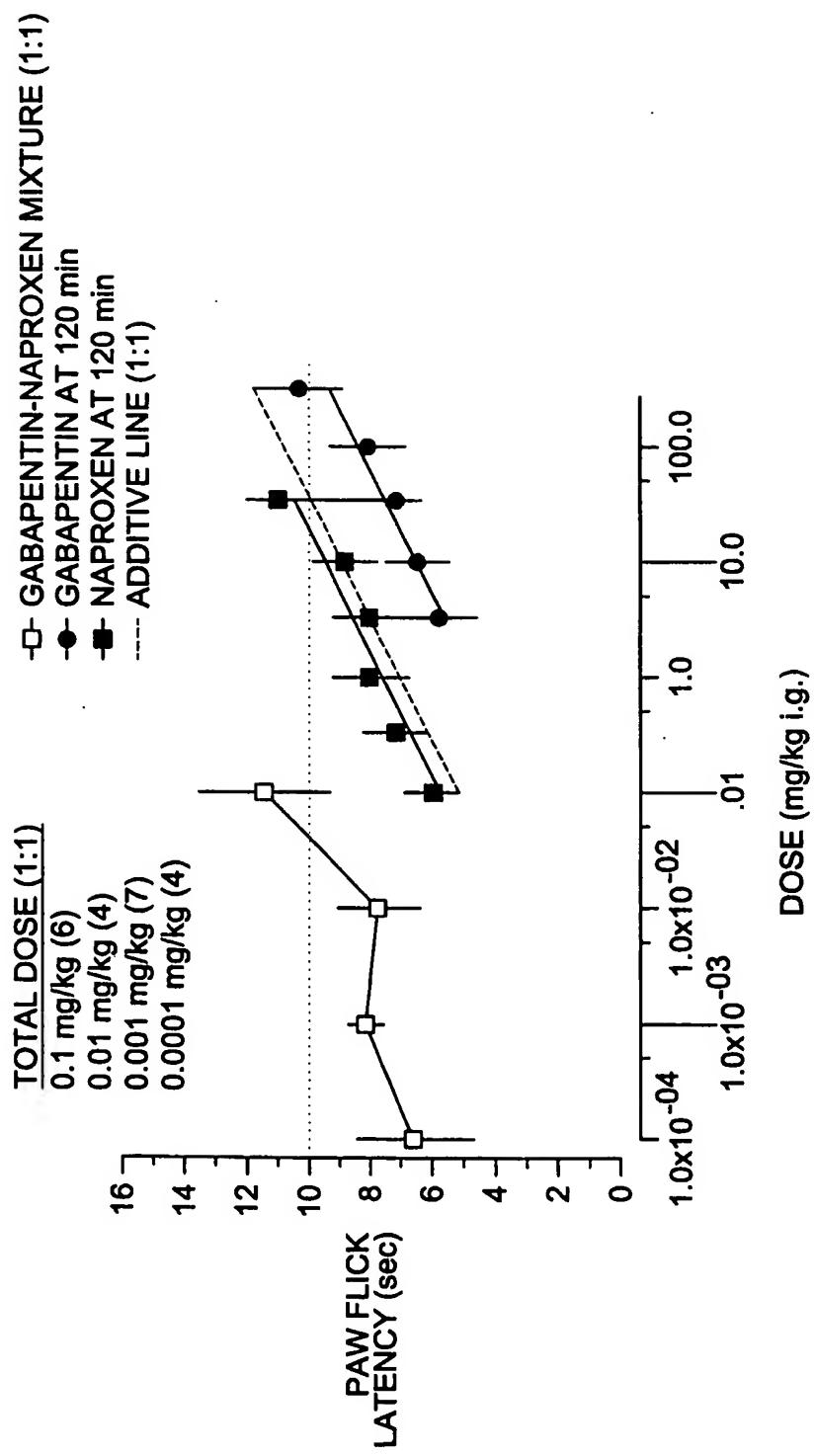
5. The combination of Claim 1 wherein the anti-epileptic compound is pregabalin.
5. 6. A combination of an effective amount of at least one anti-epileptic compound having pain alleviating properties and an effective amount of a NMDA receptor antagonist.
7. The combination of Claim 6 wherein the anti-epileptic compound is gabapentin.
10. 8. The combination of Claim 6 wherein the anti-epileptic compound is pregabalin.
9. A combination of an effective amount of at least one anti-epileptic compound having pain alleviating properties and an effective amount of a NSAID.
15. 10. The combination of Claim 9 wherein the anti-epileptic compound is gabapentin.
11. The combination of Claim 9 wherein the anti-epileptic compound is pregabalin.
20. 12. The combination of Claim 9 wherein the anti-epileptic compound is NSAID is naproxen.
13. A combination of an effective amount of at least one anti-epileptic compound having pain alleviating properties and an effective amount of a narcotic analgesic.

-17-

14. The combination of Claim 13 wherein the anti-epileptic compound is gabapentin.
15. The combination of Claim 13 wherein the anti-epileptic compound is pregabalin.
- 5 16. The combination of an effective amount of at least one anti-epileptic compound having pain alleviating properties and an effective amount of two or more compounds selected from the group consisting of NMDA receptor antagonists, analgesics, NSAIDs, and combinations thereof.
- 10 17. The combination of Claim 16 wherein two compounds are selected from the group consisting of NMDA receptor antagonists, analgesics, NSAIDs, and combinations thereof.
18. The combination of Claim 17 wherein the two compounds are an analgesic and an NSAID.
- 15 19. The combination of Claim 18 wherein the two compounds are a opioid and an NSAID.
20. The combination of Claim 19 wherein the two compounds are morphine and naproxen.
21. The combination of Claim 16 wherein the anti-epileptic compound is gabapentin.

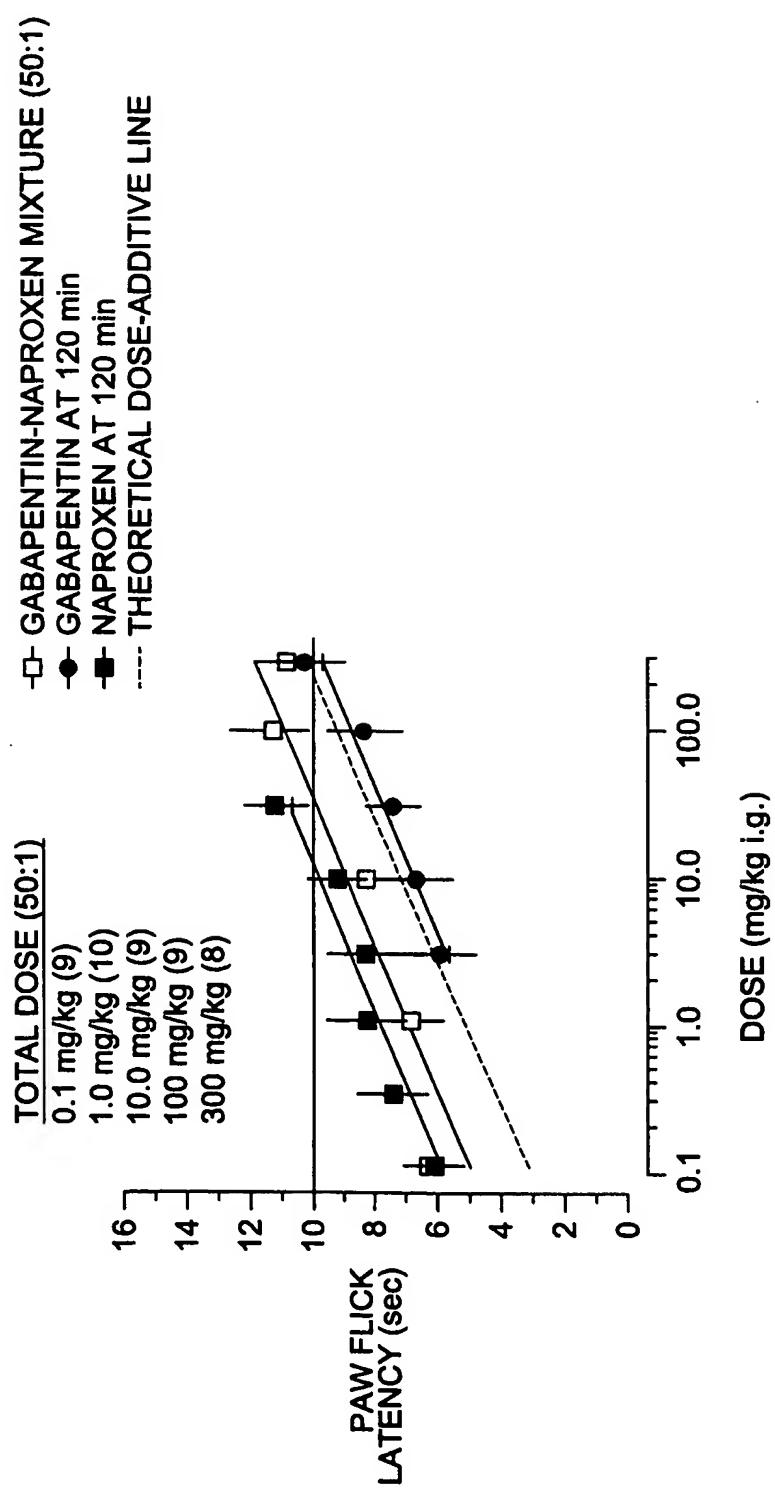
1/2

FIG. 1



2/2

FIG. 2



INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/02080

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61K31/195

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 99 12537 A (WARNER LAMBERT CO ;MAGNUS MILLER LESLIE (US); SALTEL DOUGLAS A (US) 18 March 1999 (1999-03-18) the whole document ----	1-16, 21
X	WO 99 08670 A (BUENO LIONEL ;CHOVET MARIA (FR); DIOP LAURENT (FR); LITTLE HILARY) 25 February 1999 (1999-02-25) page 6, line 4 - line 21 ----	1-12
X	WO 98 07447 A (LYLE JOHN W ;CARUSO FRANK S (US); MINN FREDRICK L (US); ALGOS PHAR) 26 February 1998 (1998-02-26) page 3, line 29 -page 4, line 25 claims ----	1-3, 6, 7, 13, 14
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- X document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- ? document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- S document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 July 2000	25/07/2000
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel: (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Authorized officer Leherte, C

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/US 00/02080

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>REN ET AL: "effects of gabapentin on indomethacin-induced and ethanol-induced gastric injury" <i>GASTROENTEROLOGY</i>, US, ELSEVIER, NEW YORK, NY,, vol. 114, no. 4, 15 April 1998 (1998-04-15), page 26 XP002081397 ISSN: 0016-5085 the whole document</p> <p>---</p>	1-3,9,10
X	<p>LESCH ET AL: "the gaba-derivative 3-isobutyl gaba acts centrally to protect against indomethacin-induced gastric damage in rats" <i>GASTROENTEROLOGY</i>, US, ELSEVIER, NEW YORK, NY,, vol. 114, no. 4, 15 April 1998 (1998-04-15), page 200 XP002081396 ISSN: 0016-5085 the whole document</p> <p>---</p>	1,4,5,9, 11
X	<p>WO 87 01036 A (UNIV NEW YORK) 26 February 1987 (1987-02-26) page 5, line 18 - line 22</p> <p>-----</p>	1,6

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-21

Present claims 1-21 relate to a combination defined by reference to a desirable characteristics or properties, namely "anti-epileptic compounds having pain alleviating properties", "NMDA receptor antagonists", "NSAIDs", "(narcotic) analgesics" and "opioids".

The claims cover all combinations containing compounds having those characteristic or properties, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such combinations. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the combinations by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the combination mentioned in the example of the description at page 10, with due regard to the general idea underlying the application.

The subject matter of claim 12 is not clear.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members			International Application No	
Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9912537	A 18-03-1999	AU 9198798 A EP 1011658 A NO 20001175 A ZA 9808159 A		29-03-1999 28-06-2000 07-03-2000 11-03-1999
WO 9908670	A 25-02-1999	AU 8668598 A AU 9293098 A EP 1009399 A NO 20000786 A WO 9908671 A		08-03-1999 08-03-1999 21-06-2000 17-02-2000 25-02-1999
WO 9807447	A 26-02-1998	AU 4078897 A EP 0942752 A		06-03-1998 22-09-1999
WO 8701036	A 26-02-1987	US 4694010 A AU 579028 B AU 6283786 A DK 178687 A EP 0233932 A JP 63500598 T US 4898860 A ZA 8606194 A		15-09-1987 10-11-1988 10-03-1987 08-04-1987 02-09-1987 03-03-1988 06-02-1990 29-04-1987

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31 /195, 31 /52		A1	(11) International Publication Number: WO 00/02592 (43) International Publication Date: 20 January 2000 (20.01.00)
(21) International Application Number: PCT/US99/13947 (22) International Filing Date: 18 June 1999 (18.06.99) (30) Priority Data: 60/092,171 9 July 1998 (09.07.98) US		(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES/FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(71) Applicant (<i>for all designated States except US</i>): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventors; and (75) Inventors/Applicants (<i>for US only</i>): MAGNUS, Leslie [US/US]; 68 Rockledge Drive, Livingston, NJ 07039 (US). SEGAL, Catherine, A. [US/US]; 5 Dogwood Drive, Chester, NJ 07930-2707 (US). (74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.			
(54) Title: PHARMACEUTICAL COMPOSITION CONTAININIG GABA ANALOGS AND AN ANTIVIRAL AGENT TO TREAT SHINGLES			
(57) Abstract			
<p>The present invention is a method of using certain analogs of glutamic acid and gamma-aminobutyric acid in combination with an anti-viral agent to treat shingles.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon			PT	Portugal		
CN	China	KR	Republic of Korea	RO	Romania		
CU	Cuba	KZ	Kazakhstan	RU	Russian Federation		
CZ	Czech Republic	LC	Saint Lucia	SD	Sudan		
DE	Germany	LI	Liechtenstein	SE	Sweden		
DK	Denmark	LK	Sri Lanka	SG	Singapore		
EE	Estonia	LR	Liberia				

PHARMACEUTICAL COMPOSITION CONTAINING GABA ANALOGS AND AN ANTIVIRAL AGENT TO TREAT SHINGLES

BACKGROUND OF THE INVENTION

1. Field Of The Invention

5 The present invention relates to the use of analogs of glutamic acid and gamma-aminobutyric acid (GABA) in combination with an antiviral agent, for the treatment of shingles.

2. Description of Related Art

10 The GABA analogs used in the present invention are known agents useful in antiseizure therapy for central nervous system disorders such as epilepsy, Huntington's chorea, cerebral ischemia, Parkinson's disease, tardive dyskinesia, and spasticity. It has also been suggested that the compounds can be used as 15 antidepressants, anxiolytics, and antipsychotics. See WO 92/09560 (United States Serial Number 618,692 filed November 27, 1990) and WP 93/23383 (United States Serial Number 886,080 filed May 20, 1992).

15

WO 97/33858 teaches that compounds related to gabapentin are useful or treating epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, and neuropathological disorders. WO 97/33858 does not specify what forms of pain 20 are treated.

25 Additionally, the GABA analogs compounds of the present invention are known for treatment of neuropathic pain. For example, see Rosner H; Rubin L; Kestenbaum A., Gabapentin adjunctive therapy in neuropathic pain states. Clin J Pain, 1996 Mar, 12:1, 56-8; Segal AZ; Rordorf G., Gabapentin as a novel treatment for postherpetic neuralgia. Neurology, 1996 Apr, 46:4, 1175-6; Wetzel CH; Connelly JF., Use of gabapentin in pain management. Ann Pharmacother, 1997 Sep, 31:9, 1082-3; Zapp JJ., Postpoliomyelitis pain treated with gabapentin [letter]. Am Fam Physician, 1996 Jun, 53:8, 2442, 2445; Cheville A, et al., 30 Neuropathic pain in radiation myelopathy:a case report. Program book, American

Pain Society (14th Annual Scientific Meeting). Abstract #95823, p. A-115; Sist T; Filadora V; Miner M; Lema M., Gabapentin for idiopathic trigeminal neuralgia: report of two cases. Neurology, 1997 May, 48:5, 1467; Waldman SD, Tutorial 28: Evaluation and Treatment of Trigeminal Neuralgia. Pain Digest 5 (1997) 7:21-24; Mellick LB; Mellick GA., Successful treatment of reflex sympathetic dystrophy with gabapentin [letter]. Am J Emerg Med, 1995 Jan, 13:1, 96; Mellick GA; Seng MI., The use of gabapentin in the treatment of reflex sympathetic dystrophy and a phobic disorder. Am J Pain Manage 1995; 5:7-9; Mellick GA; Mellicy LB; Mellick LB., Gabapentin in the management of reflex sympathetic dystrophy [letter]. J Pain Symptom Manage, 1995 May, 10:4, 265-6; Mellick GA; Mellick LB., Reflex sympathetic dystrophy treated with gabapentin. Arch Phys Med Rehabil, 1997 Jan, 78:1, 98-105 and Mackin GA., Medical and pharmacologic management of upper extremity neuropathic pain syndromes. J Hand Ther, 1997 Apr-Jun, 10:2, 96-109.

15

U.S. Patent No. 5,589,180 teaches a plaster composition for treating pain from herpes zoster or post herpetic neuralgia comprising an adhesive containing 2-10% by weight lidocaine, at least one of propylene glycol and glycerin as a co-solvent and a covering.

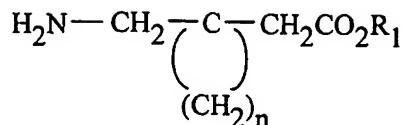
20

Antiviral compounds are known to treat herpes. These compounds include acyclovir, famciclovir, valacyclovir, penciclovir and mixtures thereof. These antiviral compounds interfere with the enzyme thymidine kinase that is needed to for the replication of the herpes virus.

25

SUMMARY OF THE INVENTION

This invention provides a method for treating shingles comprising administering to a subject suffering from shingles an effective amount of a GABA analog and an antiviral agent. A preferred embodiment utilizes a cyclic amino acid compound of Formula I

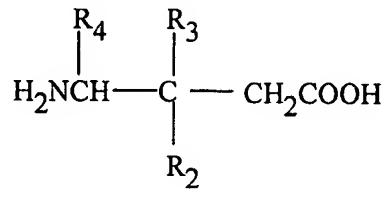


I

wherein R₁ is hydrogen or lower alkyl and n is an integer of from 4 to 6, and the pharmaceutically acceptable salts thereof. An especially preferred embodiment utilizes a compound of Formula I where R₁ is hydrogen and n is 4, which compound is 1-(aminomethyl)-cyclohexane acetic acid, known generically as gabapentin.

In another embodiment, the invention includes treating shingles with a compound of Formula II and an antiviral agent.

10 Formula II



II

wherein R₂ is a straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl having from 3 to 6 carbon atoms; R₃ is hydrogen or methyl; and R₄ is hydrogen, methyl, or carboxyl; or an individual enantiomeric isomer thereof; or a pharmaceutically acceptable salt thereof, in unit dosage form, to a mammal in need of said treatment.

Preferred compounds of the invention are those wherein R₄ and R₃ are hydrogen, and R₂ is -(CH₂)_{0-2-i}C₄H₉ as an (R), (S), or (R,S) isomer.

The more preferred compounds of Formula II invention are (S)-3-(aminomethyl)-5-methylhexanoic acid and 3-aminomethyl-5-methyl-hexanoic acid, now known generically as pregabalin.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The method of this invention utilizes any GABA analog. A GABA analog is any compound derived from or based upon gamma-aminobutyric acid. The compounds are readily available, either commercially, or by synthetic methodology well-known to those skilled in the art of organic chemistry. The preferred GABA analogs to be utilized in the method of this invention are cyclic amino acids of Formula I. These are described in U.S. Patent 4,024,175, which is incorporated herein by reference. Another preferred method utilizes the GABA analogs of Formula II, and these are described in U.S. Patent 5,563,175 which is incorporated herein by reference.

All that is required to practice the method of this invention is to administer a GABA analog in an amount that is effective to treat shingles. Such amounts will generally be from about 1 to about 300 mg per kg of subject body weight. Typical doses will be from about 10 to about 5000 mg per day for an adult subject of normal weight. It is expected that common doses that might be administered could be from 100 mg three times a day up to 600 mg four times a day. Commercially available capsules of 100 mg, 300 mg, and 400 mg of gabapentin can be administered. Alternate forms include liquids and film-coated tablets.

20

If a compound of Formula II, such as pregabalin is used, the dosage level is one sixth that of gabapentin. The dosage range for pregabalin is from about 0.15 mg to about 50 mg per kg per day of subject body weight. Typical dosages for pregabalin will be from about 1.6 mg to about 840 mg per day with individual dosages ranging from about 0.15 mg to about 65 mg per dose.

30

The compounds of the present invention may form pharmaceutically acceptable salts with both organic and inorganic acids or bases. For example, the acid addition salts of the basic compounds are prepared either by dissolving the free base in aqueous or aqueous alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution. Examples of pharmaceutically acceptable salts are hydrochlorides,

hydrobromides, hydrosulfates, etc. as well as sodium, potassium, and magnesium, etc. salts.

5 The compounds of the Formula II can contain one or several asymmetric carbon atoms. The invention includes the individual diastereomers or enantiomers, and the mixtures thereof. The individual diastereomers or enantiomers may be prepared or isolated by methods already well-known in the art.

10 Pharmaceutical compositions of the compound of the present invention or its salts are produced by formulating the active compound in dosage unit form with a pharmaceutical carrier. Some examples of dosage unit forms are tablets, capsules, pills, powders, aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions packaged in containers containing either one or some larger number of dosage units and capable of being subdivided into individual doses. Some examples of suitable pharmaceutical carriers, including pharmaceutical diluents, are gelatin capsules; sugars such as lactose and sucrose; starches such as corn starch and potato starch, cellulose derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, methyl cellulose, and cellulose acetate phthalate; gelatin; talc; stearic acid; magnesium stearate; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and oil of theobroma; propylene glycol, glycerin; sorbitol; polyethylene glycol; water; agar; alginic acid; isotonic saline, and phosphate buffer solutions; as well as other compatible substances normally used in pharmaceutical formulations. The compositions of the invention can also contain other components such as coloring agents, flavoring agents, and/or preservatives. These materials, if present, are usually used in relatively small amounts. The compositions can, if desired, also contain other therapeutic agents.

15 20 25

30 The percentage of the active ingredients in the foregoing compositions can be varied within wide limits, but for practical purposes it is preferably present in a concentration of at least 10% in a solid composition and at least 2% in a primary liquid composition. The most satisfactory compositions are those in which a much higher proportion of the active ingredient is present.

Routes of administration of the subject compound or its salts are oral or parenteral. For example, a useful intravenous dose is between 5 and 50 mg and a useful oral dosage is between 20 and 800 mg. The dosage is within the dosing range used in treatment of pain or as would be with the needs of the patient as described by the physician.

A unit dosage form of the GABA analog to be used in this invention may also comprise other compounds useful in the treatment of pain.

10

The advantages of using the compounds of Formula I and II, especially gabapentin and pregabalin, in the instant invention include the relatively nontoxic nature of the compounds, the ease of preparation, the fact that the compounds are well-tolerated, and the ease of IV administration of the drugs. Gabapentin has few interactions with major classes of drugs since it is not metabolized in the liver, but rather excreted unchanged from the body. Further, the drugs are not metabolized in the body. The subjects treated with the method of the present invention are mammals, including humans.

15

The antiviral compositions used in the present invention reduce the viral load thereby reducing the number of days of suffering. GABA analogs have no direct impact on the viral load. The GABA analogs work to diminish the pain signals begin transmitted from the peripheral nerves to the brain. The combination of actions improve control and pain relief during a shingles infection.

20

25

We claim:

1. A method for treating sinus headache or sinus pain, comprising
administering a pharmaceutical composition comprising:

(a) an analgesically effective amount of a GABA analog; and

(b) an effective amount of a anti-viral agent.

2. The method according to claim 1, wherein the GABA analog is the compound according to Formula I:

$$\begin{array}{c} \text{H}_2\text{N}—\text{CH}_2—\overset{\text{C}}{\underset{(\text{CH}_2)_n}{\textcirclearrowright}}\text{CH}_2\text{CO}_2\text{R}_1 \\ \text{I} \end{array}$$

wherein R_1 is hydrogen or lower alkyl and n is an integer of from 4 to 6, and the pharmaceutically acceptable salts thereof.

3. The method according to claim 2, wherein Formula I comprises gabapentin.

4. The method according to claim 1, wherein the anti-viral agent is selected from the group consisting of acyclovir, famciclovir, valacyclovir, peniclovir and mixtures thereof.

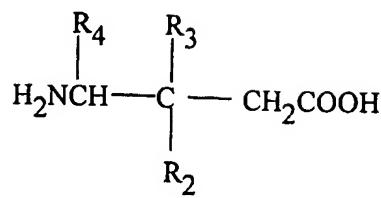
5. The method according to claim 2, comprising from about 10 mg to about 400 mg of Formula I.

6. The method according to claim 3, comprising from about 10 mg to about 400 mg of gabapentin.

7. The method according to claim 3, comprising from about 10 mg to about 400 mg of gabapentin and from about 60 mg to about 200 mg of anti-viral agent.

8. The method according to claim 1, wherein the GABA analog is a

compound according to Formula II:



II

wherein R₂ is a straight or branched alkyl of from 1 to 6 carbon atoms,
 5 phenyl, or cycloalkyl having from 3 to 6 carbon atoms; R₃ is hydrogen or methyl;
 and R₄ is hydrogen, methyl, or carboxyl.

9. The method according to claim 8, wherein Formula II comprises pregabalin.

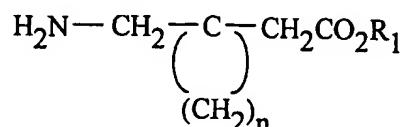
10. The method according to claim 8, comprising from about 0.15 mg
 10 to about 65 mg of Formula II.

11. The method according to claim 9, comprising from about 0.15 mg
 to about 65 mg of pregabalin.

12. A composition for eliciting an enhanced analgesic response in a
 mammal comprising:

- 15 (a) an analgesically effective amount of a GABA analog; and
 (b) an effective amount of a anti-viral agent.

13. The composition according to claim 12, wherein the GABA analog
 the compound according to Formula I:



I

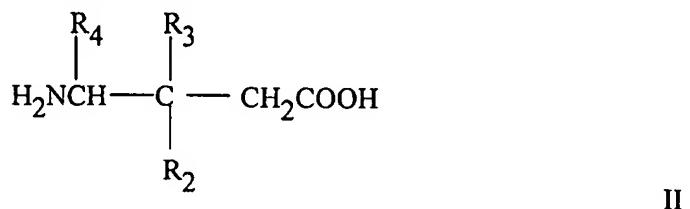
20 wherein R₁ is hydrogen or lower alkyl and n is an integer of from 4 to 6, and the
 pharmaceutically acceptable salts thereof.

14. The composition method according to claim 13, wherein Formula I comprises gabapentin.

15. The composition according to claim 13, comprising from about 10 mg to about 400 mg of Formula I.

5 16. The composition according to claim 14, comprising from about 10 mg to about 400 mg of gabapentin.

17. The composition according to claim 12, wherein the GABA analog is a compound according to Formula II:



10 wherein R₂ is a straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl having from 3 to 6 carbon atoms; R₃ is hydrogen or methyl; and R₄ is hydrogen, methyl, or carboxyl.

15 18. The composition according to claim 17, wherein Formula II comprises pregabalin.

19. The composition according to claim 17, comprising from about 0.15 mg to about 65 mg of Formula II.

20. The composition according to claim 19, comprising from about 0.15 mg to about 65 mg of pregabalin.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/13947

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/195 A61K31/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GB 2 282 759 A (SMITHKLINE BEECHAM PLC) 19 April 1995 (1995-04-19) claims 1-9 ---	1-20
Y	WO 98 03167 A (WARNER-LAMBERT COMPANY) 29 January 1998 (1998-01-29) claims 1-15 ---	1-20
Y	WO 95 09632 A (SMITHKLINE BEECHAM PLC) 13 April 1995 (1995-04-13) claims 1-13 ---	1-20
Y	ROSENBERG J M ET AL: "The effect of gabapentin on neuropathic pain" THE CLINICAL JOURNAL OF PAIN, vol. 13, no. 3, September 1997 (1997-09), pages 251-255, XP002101738 abstract ---	1-20 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 October 1999	21/10/1999
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Siatou, E

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/13947

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	R.W. JOHNSON: "Current and future management of herpes zoster" ANTIVIRAL CHEMISTRY AND CHEMOTHERAPY, vol. 8, no. S. 1, 1997, pages 19-29, XP002117663 abstract page 21, left-hand column page 25, left-hand column, line 1 - line 9 ---	1-20
A	SATTERTHWAITE J R: "ACUTE HERPES ZOSTER: DIAGNOSIS AND TREATMENT" PAIN MANAGEMENT, vol. 3, no. 1, 1 January 1990 (1990-01-01), pages 17-28, XP000574537 ISSN: 0896-9132 page 22, right-hand column, line 3 -page 23, left-hand column ---	1-20
A	NIKKELS A F ET AL: "RECOGNITION AND TREATMENT OF SHINGLES" DRUGS, vol. 48, no. 4, 1 October 1994 (1994-10-01), pages 528-548, XP000567542 ISSN: 0012-6667 page 530, right-hand column, paragraph 1.4 page 535, right-hand column, line 1 -page 536, right-hand column, line 5 page 541, right-hand column, line 1 -page 542, left-hand column, line 12 ----	1-20
A	WO 97 33859 A (WARNER-LAMBERT COMPANY) 18 September 1997 (1997-09-18) cited in the application claims 1-21 -----	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PL, US 99/13947

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
GB 2282759	A 19-04-1995	AU	7860394 A		08-05-1995
		BE	1007586 A		16-08-1995
		CA	2174240 A		27-04-1995
		EP	0723448 A		31-07-1996
		FR	2711061 A		21-04-1995
		WO	9511027 A		27-04-1995
		JP	9503779 T		15-04-1997
		ZA	9408065 A		10-04-1996
-----	-----	-----	-----	-----	-----
WO 9803167	A 29-01-1998	AU	3602497 A		10-02-1998
		EP	0934061 A		11-08-1999
		HR	970387 A		31-10-1998
		NO	990279 A		22-01-1999
		PL	331325 A		05-07-1999
-----	-----	-----	-----	-----	-----
WO 9509632	A 13-04-1995	AP	616 A		15-09-1997
		AU	7788494 A		01-05-1995
		CA	2173505 A		13-04-1995
		CN	1135180 A		06-11-1996
		EP	0804199 A		05-11-1997
		HU	74076 A		28-10-1996
		IL	111138 A		15-04-1997
		JP	10513434 T		22-12-1998
		US	5866581 A		02-02-1999
		ZA	9407738 A		10-08-1995
		SG	49291 A		18-05-1998
-----	-----	-----	-----	-----	-----
WO 9733859	A 18-09-1997	AU	2127197 A		01-10-1997
		CA	2245647 A		18-09-1997
		CZ	9802875 A		17-02-1999
		EP	0888285 A		07-01-1999
		NO	984204 A		11-09-1998
		PL	328800 A		15-02-1999
		SK	124898 A		11-02-1999